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Leaky Gut and Leaky Calves: Umbrella Review for Evidence of Proof and Published Articles

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Abstract

In the present article we, as presenting authors write an umbrella review for detailed determination of 'leaky gut', 'intestinal permeability', 'zonulin' and for better understanding for the readers. Tight junctions, describing foremost barrier within the paracellular route among intestinal epithelial cells. Disturbed tight junctions consequently alter intestinal hyperpermeability (namely "leaky gut") and has been linked to the proposed pathogenesis of several different disorders also among calves and cattle. The aim was to write an umbrella review providing an overview of proof of evidence for participation of leaky gut and related zonulin levels also involving tight junction breakdown. Several studies were summarized, which could have helped better basic understanding of this disruption and its relevant mechanistic consequences. Taking into account those data, veterinary surgeons could probably lead to prevention/treatment of several different disorders by using nutritional additives, which were also briefly explained at this manuscript also.

Keywords: Calf, Intestinal Permeability, Leaky Gut, Zonulin.

Sızıntılı Bağırsak Sendromu ve Sızıntılı Buzağılar: Kanıt Düzeyi ve Literatürün Şemsiye Derlemesi

Öz

Bu makalede, biz sunan yazarlar olarak, okuyucular için daha iyi bir anlayış sağlamak amacıyla "sızıntılı bağırsak", "intestinal geçirgenlik" ve "zonulin"in ayrıntılı belirlenmesi için bir şemsiye derleme yazdık. Sıkı bağlantılar, intestinal epitel hücreleri arasındaki paraselüler yolun başlıca bariyerini oluşturur. Sıkı bağlantı bütünlüğünün bozulması, intestinal hiperpermeabiliteye (diğer adıyla 'sızıntılı bağırsak') yol açmakta olup, bu mekanizma, buzağılar ve sığırlar dâhil olmak üzere birçok farklı hastalığın patogenezi ile ilişkilendirilmiştir. Bu çalışmanın amacı, sızıntılı bağırsak oluşumu, buna eşlik eden zonulin düzeyleri ve sıkı bağlantı bozulmasını kapsayan kanıtlara genel bir bakış sunan bir şemsiye derleme hazırlamaktır. Bu bozulma ve ilişkili mekanistik sonuçların daha iyi anlaşılmasına katkı sağlayacak çalışmalar derlenmiştir. Bu veriler dikkate alındığında, veteriner hekimlerin bu makalede ayrıca kısaca açıklanan besinsel katkı maddelerini kullanarak çeşitli hastalıkların önlenmesi ve/veya tedavisine katkı sağlayabilecekleri düşünülmektedir.

Anahtar Kelimeler: Buzağı, İntestinal Geçirgenlik, Sızıntılı Bağırsak, Zonulin.

Introduction

The intestinal barrier is a multiplex network composed of mucus layer, epithelial cell and basal lamina propria. Given physical barrier of intestinal microbiota, constituted by tight junctions multi-protein intricate. Disrupted tight junctions elevated epithelial permeability, consequently leading to leaky gut (Cereijido and Anderson, 2001; Takeuchi et al., 2004; Liu et al., 2005; Quigley, 2016; Nagpal and Yadav, 2017; Camilleri, 2019; Moonwiriyakit et al., 2023). Fig. 1 showed brief and shortened mechanistic value of this study along with self-archive 2 calves (one diseased and other healthy one). Considering gastrointestinal barrier, which has been described as a pivotal defender for maintenance of epithelial cell integrity, and thus prevention against infections along with diminished inflammation (van Zyl et al., 2020). Deficient nutrition might suppress immune functioning and elevated the probability of infection and disease (Nonnecke et al., 2003). It is also denoted that nutrition has a pivotal role for regulating intestinal development, as well as health status of the calf, growth, and production traits (Fischer et al., 2019). Apart from nutrition multiple drug usage is another problematic era. In a recently fresh field study, 59 calves residing at different farms subjected to polypharmacy had been classified as diarrhea (Group I; n=20) and/or pneumonia (Group II; n=20) and 19 other healthy calves were involved as the control group (III).

Serum diamine oxidase values were detected as 8.22±2.02, 11.44 ± 1.96 and 28.90 ± 3.59 ($p < 0.001$) in Groups I, II and III, respectively. It was suggested that intestinal mucosal injury might exist in both disease activity linked to polypharmacy for at least 1 week (Alıç Ural, 2025a).

Materials and Methods

Several indexes were searched with relevant keywords, which involved 'leaky gut', 'intestinal permeability', 'intestinal epithelial cells', 'zonulin', 'intestinal integrity' etc. To those of both national and international case reports, studies or reviews were analyzed. Inclusion criteria evolved 'calves or cattle' as common denominators. To those of fulfilling criteria, solely relevant literature was composed.

Results and Discussion

Leaky gut denominator studies

In an interesting article, giardiasis, one of the foremost and wisely denoted parasitic disease, and its relationship with leaky gut was determined. In a total of eleven calves in each group [healthy control vs. diarrheic calves with mono giardia infection] were enrolled. Commercially available and obtained ELISA tests exhibited elevated mean serum zonulin levels (63.35±3.73 ng/mL vs. 34.94±3.72 ng/mL among diarrheic calves with giardiasis and healthy calves respectively). Available data obtained from that research revealed occurrence of leaky gut and altered intestinal permeability among diarrheic calves with giardiasis (Alıç Ural, 2022a).

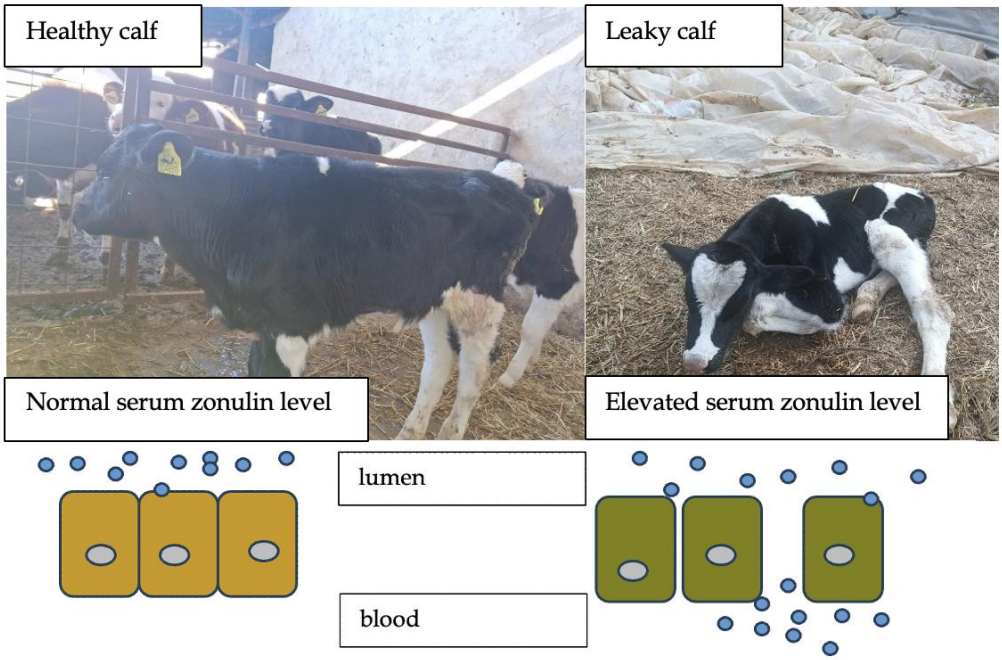

Fig. 1. Authors self-photograph archive at Intestinal Permeability Measurement Center (İPÖM) depicting one healthy calf and another one on the right side as a leaky calf with leaky gut. Elevated serum zonulin level indicated altered intestinal permeability and leaky gut.

In prior research multiple repeated either low or high dose intramuscular indomethacin administration (every 12 h for 48 h) was inducted for mimicking leaky gut in 18 male, 2-4 days old Holstein calves. The investigators aimed at detecting fatal effects of leaky gut on intestinal tissue functioning and inflammatory respond. In that study biomarkers of intestinal permeability (prior to and thereafter lactulose, d-mannitol, and chromium-EDTA consumption), several cytokines were analyzed. At the end of the trial calves were sacrificed. The variance for biomarker levels among pre and post challenges was elevated in indomethacine administered calves (for lactulose and chromium-EDTA). Moreover, chemokine ligand 2/4 and IL-6 were elevated among high dose indomethacine group of calves. Furthermore, both high and low doses of indomethacin caused deduced villus length and surface area through distal jejunum and ileum. There were also diminished crypt depth and width throughout colon. In that interesting trial it was shown that repeated indomethacin injections through 48-h caused leaky-gut-like clinical signs, negatively influencing distal portion of the bowel (Cangiano et al., 2022). This trial of leaky gut model, established at that trial could reflect the importance of intestinal health and avoidance of indomethacine and relevant drugs (Cangiano et al., 2022).

A significant study was performed with the hypothesis of probable intestinal barrier integrity disruption associated with heat stress causing leaky gut in cattle. In that research in an attempt to exhibit intestinal barrier disruption via heat stress, serum zonulin levels were analyzed. The study protocol involved a local farm in Aydın, Türkiye through August (36-44°C, %36 humidity). Serum zonulin (ng/ml) concentrations were elevated (60.07 ± 21,20) at mid night in comparison to mid-day (34.60 ± 10.90) (p=0.018). Elevated zonulin concentration were deemed linked to altered intestinal barrier/intestinal permeability due to heat stress (Alıç Ural et al., 2021a).

Zonulin search in advance literature with special reference to ruminants

Zonulin investigation has been targeted in several previous article (Alıç Ural et al., 2021a; Alıç Ural et al., 2021b; Alıç Ural, 2022a; Alıç Ural, 2022b; Alıç Ural et al., 2022; Alıç Ural, 2022c; Alıç Ural, 2023; Alıç Ural and Ural, 2023; Alıç Ural, 2025a) on ruminants, those of which were performed in Türkiye.

In a field investigation describing 'gut-lung axis' in calves with respiratory distress syndrome it was hypothesized that this axis has relationship with leaky gut and intestinal permeability. For this purpose, relevant field study determining gut-lung axis in 78 calves [n=59 with respiratory distress syndrome and n=19 healthy] belonging to 5 different milk-fed veal commercial farms were enrolled. The mean zonulin levels (ng/mL) in calves exhibiting respiratory distress were detected as 66.71± 4.602 with significant elevation in comparison to healthy calves 21.69±4.234 ($p<0.05$) (Erdogan et al., 2024)

It was hypothesized that elevated intestinal permeability among rotavirus-linked diarrhea has to be elucidated. In that article 25 calves (n=10 with diarrhea and mono-infected with rotavirus, 8 calves co-infected with rotavirus and other agents and 7 other healthy) mean±standart error serum zonulin levels (ng/mL) were increased in both mono- and co-infected calves in comparison to healthy calves, suggesting elevated intestinal permeability indicating diagnosis of leaky gut (Alıç Ural, 2025d).

Intestinal health repair via nutraceuticals

Phytotherapeutical and of relevant nutraceuticals have arousing interest for the last years also involving calves health and welfare. For his part, the authors would focus on intestinal health and related investigations, specifically targeted at natural products at treat to target focus.

Turmeric, as extracted from *Curcuma longa L.*, and its relevant influence on leaky gut (serum zonulin concentrations), fecal consistency and latent cleansing scores among diarrheic calves, were investigated in Türkiye. Four different commercial farms were evolved and n=19 calves from each farm with diarrhea were selected and enrolled. Sandwich ELISA was preferred in an attempt to calculate zonulin levels. In that research diarrhea was described with a stool score ≥2-3. Curcumin treatment resulted with significantly ($p <0.001$) altered stool scores and diminished zonulin levels ($p <0.001$), indicating its influence on diminishing leaky gut (Alıç Ural, 2025b).

A prior field study regarding diarrheic (n=11) and non-diarrheic (n=7), healthy calves aimed at analyzing the efficacy of citrus seed extract, on hide cleanliness and stool consistency scores. Following interpretation of stool consistency and hide cleanliness, scored at 0 to 3, citrus seed extract was given in rectal enema for seven days. Both stool consistency and hide cleanliness scores were diminished and detected at 0 to 1, suggesting intestinal health support among calves with diarrhea (Alıç Ural et al., 2022). Another recent study supported the efficacy of urolithin-a on calves intestinal health. In that investigation urolithin-a caused diminished diarrheic days and latent cleanliness scores, linked to anti-inflammatory and immunomodulatory effects (Alıç Ural, 2025c).

Conclusion

The intestinal barrier is essential for maintaining gut integrity, preventing infections, and supporting overall health in calves. Disruption of this barrier leads to leaky gut, which can result from stress, infection, or drug exposure. Early detection and intervention are key to minimizing intestinal damage. Nutritional and

phytotherapeutic approaches, such as curcumin, citrus seed extract, and urolithin-A, have shown promising effects in restoring gut integrity, improving fecal consistency, and supporting overall calf health. Maintaining a healthy intestinal barrier is therefore critical for animal welfare, growth, and productivity.

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